Updated August 2006

TO: South Carolina Physicians and Clinical Laboratories
FROM: South Carolina Department of Health and Environmental Control
Division of Acute Epidemiology and Bureau of Laboratories (BOL)
SUBJECT: 1. West Nile Virus Update: Clinical Presentation, Diagnostic Testing available through DHEC, Specimen Submission & Reporting, Internet Resources
2. Related Information Regarding Eastern Equine Encephalitis and Enteroviral Aseptic Meningitis

1. Introduction -- In North America West Nile Virus (WNV), a mosquito-borne flavivirus infection, was first identified in the fall of 1999 in a relatively localized outbreak in New York City and neighboring counties. Since then the virus has spread dramatically across the entire continental United States and, in 2002, over 2000 cases of WNV human neuroinvasive disease were reported in 44 of the 48 continental states. Although the vast majority of cases result from the bite of infected mosquitoes, several new modes of transmission were identified in 2002 including transmission via organ transplantation, blood transfusion, laboratory accidents, and mother-to-child transmission both transplacental and via breast milk. In South Carolina, the presence of WNV is monitored through mosquito trapping surveillance, as well as reported cases in humans and animals (especially sick equine and dead wild birds).

In 2003 the first human case occurred in June and the last case occurred in November, making a total of six human cases. Three of the six cases had neuroinvasive disease. In 2003 WNV was identified in 282 bird specimens, 1 alpaca, 54 horses and 3 mosquito pools. In 2004, there was one confirmed and one probable human case of West Nile fever. In 2004, WNV was detected in 21 birds, and one mosquito pool. In 2005, there were four human neuroinvasive cases, no equine and 15 mosquito pools. Thus far in 2006 as of July, there has been one WNV positive blue jay found in Charleston county.

The Eastern Equine Encephalitis (EEE) virus (togavirus family) has long been recognized in the United States, though fewer than 160 cases have been reported in humans in this country in the past 35 years. However, to date this year, nearly 100 equine cases have been reported in South Carolina and EEE virus has also been isolated from birds and mosquitoes. In 2003, there were two probable human cases of EEE in Lexington and Bamberg County, respectively. There were one human case of EEE in 2004.

2. WNV Clinical Syndromes (See also: CDC's clinical fact sheet)
WNV infection can lead to spectrum of syndromes ranging from severe encephalitis and aseptic meningitis to a relatively mild non-specific febrile illness and, most commonly, to asymptomatic infection.

- **Neuroinvasive Disease (Encephalitis, Meningitis or poliomyelitis):** Severe neurological disease is seen in approximately one of 150 WNV infections, most commonly in patients over 50 years of age. The most common presentation is that of a viral encephalitis presenting with fever, change in mental status and, in some cases, weakness, and gastrointestinal symptoms occasionally accompanied by a rash involving the neck, trunk and extremities. Other neurological presentations have included acute flaccid paralysis, seizures and cranial nerve abnormalities. Acute flaccid paralysis otherwise known as West Nile poliomyelitis, is less common then West Nile meningitis or encephalitis.

- **Aseptic Meningitis:** This presentation is characterized by fever, headache, stiff neck, and photophobia with CSF pleocytosis and negative bacterial cultures. Patients with this presentation of WNV CNS infection will usually not be clinically distinguishable from those with aseptic meningitis due to the more commonly seen "summer enteroviruses." In that regard, it is important to note that, during 2003, enteroviral meningitis cases have appeared earlier and in greater numbers than usual. To date ECHO 9 has been the predominantly isolated pathogen (See the Clinician Advisory regarding Enterovirus Echo 9 Meningitis in South Carolina). The CDC MMWR of August 15, 2003 will include an article with national perspective about enteroviral meningitis (see www.cdc.gov/mmwr).

- **Non-Neuroinvasive (West Nile Fever)** is a non-specific, self-limited, febrile illness caused by WNV and is experienced by approximately 20 percent of infected persons. The disease generally occurs 2-6 days (range 2-15) after infection via mosquito-bite and is typically characterized by acute onset of fever, headache and myalgias. Maculopapular rash and lymphadenopathy are observed in less than 20 percent of cases. Illness typically lasts from 2 to 7 days.

- **Asymptomatic infection:** Most (~80 percent) WNV infections are asymptomatic. This explains why about 20 cases of WNV infection in 2002 resulted from blood transfusions. Those are apparently attributable to asymptomatic persons who, by chance, had been infected with WNV a few days prior to donation and were therefore experiencing a transient silent viremia just at the time of their donation. As a result of those cases, blood banks in the United States began screening blood for WNV as of July 1, 2003.

3. Diagnostic and clinical criteria for neuroinvasive and non-neuroinvasive cases. WNV neuroinvasive and non-neuroinvasive case determination clinical and laboratory criteria can be found on the CDC Arboviral neuroinvasive and non-neuroinvasive case definition.

3. Diagnostic Testing Available through DHEC -- In South Carolina, diagnostic tests for WNV infection are performed in a number of hospital and private laboratories as well as by the DHEC Bureau of Laboratories (BOL). WNV testing by the DHEC BOL will generally be done on the following:

a. Suspected Neuroinvasive disease (Viral Encephalitis or WNV compatible severe acute neurologic syndrome, e.g. acute flaccid paralysis: Submit serum and spinal fluid on all patients with suspected viral encephalitis or severe WNV neurologic manifestations.

Because cases of encephalitis are the signal events used to monitor WNV trends of human disease across the United States, the BOL encourages physicians and clinical laboratories to submit serum and spinal fluid from all such cases. Further, when tests on patients with encephalitis have been reported by other laboratories as indicating WNV infection, the DHEC BOL would also like to receive specimens for confirmatory testing. Such testing can be done either on a remaining (and properly stored) aliquot, or on repeat (convalescent) serum. Because arboviruses other than WNV can also cause encephalitis, several of the BOL CSF tests for WNV are performed in conjunction with tests for other related viruses including Eastern Equine Encephalitis (EEE) and for St. Louis Encephalitis (SLE) which is known for causing immunologic cross-reactions leading to false-positive WNV tests.

b. Suspected Neuroinvasive disease in absence of other known cause(Aseptic Meningitis): Submit specimens on selected patients as described below to DHEC. The decision to test these should be made in consultation with DHEC.

CSF from patients suspected aseptic meningitis in the absence of other known causes may be submitted to the BOL for enteroviral cultures as well as for tests for WNV and EEE. This is because WNV CNS infections tend to occur in older persons (e.g. >50 years of age), while enteroviral aseptic meningitis is more common in children and young adults (e.g. <35 years of age).

c. Suspected Non-neuroinvasive(West Nile Fever): Testing provided by DHEC. If testing done at a commercial lab, report all positives to the local health department Epidemiology staff as DHEC can provide subsequent confirmatory testing of these positive commercial lab results.

As described above, WNV can cause a mild transient self-limited febrile illness which lasts a few days and which does not require hospitalization. However, numerous other viruses (e.g. many Echo and Coxsackie viruses) may more commonly cause a few days of "summer fever" and the number of non-specific febrile episodes is so great in a community that it is neither feasible nor desirable to test them all for WNV. Also, testing at the BOL is done in batches (e.g., weekly) so that patients with short-lived febrile episodes will usually have recovered by the time test results become available. Further, where fever is actually more commonly caused by other viruses, positive tests for WNV may be more likely to be false-positive (*low predictive value of positive test in low prevalence populations*). Finally, the phenomenon of persistent IgM anti-WNV antibodies should also be considered. Whereas for most infections "early IgM antibodies" typically persist for only a few weeks or a few months, WNV IgM antibodies have been found to

persist for over a year. (See EID Vol 9. No. 3, 2003). This incompletely understood immunological phenomenon, also seen with some other flavivirus infections, can further complicate the interpretation of an isolated "positive WNV IgM antibody test". For example, a "positive WNV IgM test" performed for a mild mid-summer febrile illness might have nothing to do with the current illness but just reflect asymptomatic WNV infection acquired during the previous year's arboviral transmission season. Thus, several difficulties argue against widespread WNV testing in the setting of mild-febrile illness without overt CNS involvement.

d. Special circumstances: In certain epidemiologic settings, as in a locality experiencing a documented extensive outbreak of WNV, additional testing may be indicated according to circumstances. An instructive example of such "special testing" (www.cdc.gov/mmwr//preview/mmwrhtml/mm5003a1.htm.) comes from the greater New York City area, which was the epi-center of initial WNV activity in the United States. Several serological surveys of local residents were carried out there to help quantify the ratio of symptomatic to asymptomatic infections and thus contribute to our understanding of this infection, which is new to North America.

4. Submitting Specimens and Reporting WNV Suspects and Cases: Physicians should contact their local County Health Department's Epidemiology staff or the Division of Acute Disease Epidemiology at 803-898-0861 (pager 888-847-0902 after hours and on weekends) to report confirmed or suspect cases of WNV and to request laboratory testing by SC DHEC. For patients meeting the clinical criteria described above, arrangements can then be made for WNV testing by the DHEC Laboratory.

The physical address for shipment of specimens is: SC DHEC Bureau of Laboratories, ATTN: Virology Laboratory, 8231 Parklane Road, Columbia, SC 29223. Virology laboratory staff can be reached by phone at 803-896-0819 to discuss questions about the WNV tests. Cerebrospinal fluid specimens shipped within 24 to 48 hours of collection may be sent on cold pack; CSF specimens held for longer periods prior to shipment should be frozen. Serum may be shipped at room temperature. Commercial overnight carrier is recommended for all shipments.

Physicians with questions about testing patients who do not have (i) encephalitis or (ii) a major acute neurological syndrome (e.g. acute flaccid paralysis), or (iii) aseptic meningitis may discuss these cases with the DHEC consultant on call at 803-898-0861.

In situations where WNV testing cannot be offered by DHEC (see above) physicians may order tests through commercial laboratories.

5. Diagnostic Tests Available through DHEC

Specimen	Test	Specimen volume	Turnaround Time	*Comments*
CSF * *Total of **1.5ml** must be submitted ensures sufficient amount for testing	WNV Serology – IgM *	0.2 ml	1-2 weeks (3 day test - performed weekly)	*IgM antibodies can be detected by enzyme immunoassay (EIA) in CSF at onset of illness, and may persist for more than a year.*
	PCR	0.4 ml	24-36 hours	*Human viremia is short lived and usually absent when IgM is detectable. This test also includes screening for eastern equine encephalitis (EEE), St. Louis encephalitis (SLE), LaCrosse virus, and California encephalitis virus.*
	Viral Culture	0.4 ml	1-2 weeks	
Serum	WNV Serology – IgM & IgG *	1.5 ml for both serology and IFA	1-2 weeks (3 day test - performed weekly)	*WNV IgG is usually not detectable during the first 6 days of illness.*
	Arbovirus IFA panel		*1-2 weeks*	*Detects total antibody (IgG and IgM) against antigens of EEE, WEE, SLE, and LaCrosse viruses.*

- All positive WNV EIAs require confirmation by plaque reduction neutralization testing (PRNT). Therefore, 2 or more weeks additional time will be required to report positive serological results.
- ** A total of 1.5ml of CSF must be submitted to ensure sufficient amounts of sample for various types of testing done by the DHEC Bureau of Labs.

6. Selected Internet Resources

Please note that for most of these links you will be leaving the DHEC Web site and our disclaimer applies. We provide these links as an informational service, but do not maintain the majority of these sites.

General Information

- West Nile Virus - What you need to know (from the CDC)
- West Nile Virus - Questions and Answers
- South Carolina DHEC WNV information

Further information resources and web links

- West Nile links from the National Institutes of Health
- CDC's West Nile Virus Home Page
- WNV Home page of the United States Geological Survey (USGS)

Information for Health Professionals

- Resources for clinicians (CDC)
- Update on national testing of blood for WNV
- Case Definitions for West Nile Virus and other arboviral encephalitides

Links to selected WNV articles and abstracts from leading journals

- Neurologic Manifestations and Outcome of West Nile Virus Infection (JAMA July 23/30, 2003)
- West Nile Virus (State of the art (!!) comprehensive review in JAMA July 23/30, 2003)
- Acute Flaccid Paralysis and West Nile Virus Infection (EID Vol 9 No. 7, 2003)
- Persistence of Virus-Reactive Serum Immunoglobulin M Antibody in Confirmed West Nile Virus Encephalitis Cases (EID Vol 9 No. 3, 2003)
- West Nile Virus primer for the clinician (Ann Int Med 137(3):173-9, 2002)
- Clinical Findings of West Nile Virus Infection in Hospitalized Patients, New York and New Jersey, 2000 (EID Vol 7 No 4, 2001)

Key articles on WNV from the CDC Morbidity Mortality Weekly Report (MMWR) of 2002 through 2004

- Update: WNV Screening of Blood Donations and Transfusion-Associated Transmission (4/9/04)
- Interim Guidelines for the Evaluation of Infants Born to Mothers Infected with West Nile Virus During Pregnancy (MMWR 02/27/04)
- Provisional Surveillance Summary of The West Nile Virus Epidemic-United States, January-November 2002 (MMWR 12/20/2002)
- West Nile Virus Infection in Organ Donor and Transplant Recipients - Georgia and Florida, 2002 (MMWR 09/06/2002)
- Investigation of Blood Transfusion Recipients with West Nile Virus Infections (MMWR 09/13/2002)
- Acute Flaccid Paralysis Syndrome Associated with West Nile Virus Infection - Mississippi and Louisiana, July-August 2002 (MMWR 09/20/2002)
- Update: Investigations of West Nile Virus Infections in Recipients of Organ Transplantation and Blood Transfusion (MMWR 09/20/2002)
- Possible West Nile Virus Transmission to an Infant Through Breast Feeding - Michigan, 2002 (MMWR 10/04/2002)
- Update: Investigations of West Nile Virus Infections in Recipients of Organ Transplantation and Blood Transfusion - Michigan, 2002 (MMWR 10/04/2002)
- West Nile Virus - US, Sep 26-Oct 2, 2002, and Investigations of WNV Infections in Recipients of Blood Transfusion and Organ Transplantation (MMWR 10/04/2002)

- West Nile Virus Activity - United States, October 10-16, 2002 and Update on WNV Infections in Recipients of Blood Transfusions (MMWR 10/18/2002)
- Investigations of West Nile Virus Infections in Recipients of Blood Transfusions (MMWR 11/01/2002)
- Laboratory Acquired West Nile Virus Infections-United States, 2002 (MMWR 12/20/2002)
- Intrauterine West Nile Virus Infection - (MMWR 12/20/2002)